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Editorial

Stromal regulation of cancer growth: A balancing act in surgery

There are examples in the literature of dormant cancer cells being stimulated after tissue injury.[1–5] On the other hand, there are also reports of cancer regression following injury.[6–8] What explanation can be offered for this discrepancy? The answer may involve the stroma or connective tissue bed of solid tumour. Traditionally this stroma has been regarded mainly as a physical support for the growing cancer cells. More recently, however, there is evidence that stromal cells, many of which are immune cells, may exude active growth control of cancer. For example, macrophages have been reported to produce many growth factors.[9] These cells can also produce collagen,[10] can differentiate into fibroblast-like cells,[11,12] and it has also been suggested that macrophages can also transform into endothelial-like cells.[13] The truly multifunctional capacity of macrophages gives them the potential to play a major role in tumour growth. In addition, other immune cells such as T-cells and B-cells have been reported to produce growth factors.[14,15] Thus, stromal cell populations present in cancer tissue can be engaged in opposing functions such as paracrine growth regulation as well as the more traditional role of defense. A more comprehensive name may be needed to reflect the dual role of these stromal 'immune' cells. In fact, the reticulo-endothelial system (RES) described by Aschoff[16] over 80 years ago comes close.

Cancer develops with abnormal local growth of cells as well as stroma in the parent organ. The next step is metastatic spread. It is interesting to note that we found evidence that this metastatic spread may involve macrophage/cancer cell units[17] migrating through the vascular system and establishing new growth at distant sites. Formation of such units suggests that paracrine growth regulation may occur at a very early stage of the metastatic process. At the metastatic site, cancer cells are still dependent on the presence of stroma for support and growth. End stage cancer, on the other hand, can be composed of cells that are completely independent of stromal regulation and can grow in the peritoneal or pleural cavity as isolated cells.[18] Using such cells for the study of solid cancer growth regulation may not reflect the natural process.[18]

In the stromal dependent phase of tumour growth there is a window of opportunity to control cancer by interfering with this support. Examples are anti-angiogenic and anti-lymphagenic treatment, reducing of growth factor output, disrupting physical support, and increasing classical immunological activity, etc. Ultimately, the goal of such treatments is stromal collapse.

An analogy may be drawn between this process and the shedding of the endometrium during the menstrual cycle where collagen producing cells (fibroblast-like) during the follicular phase can transform into phagocytic cells (macrophage-like) during the menstrual phase.[19] This process is hormonally controlled. Likewise, an infection can cause drastic changes within the tumour stroma; enough to affect stromal support of cancer cells and initiate an immunological reaction, resulting in regression of cancer.[20]

We reported on a case of apparent spontaneous regression of pancreatic cancer which may serve as an example of such phenomena.[21] Briefly, a 50-year-old male presented with a history of weight loss, anorexia and discomfort after meals. Oncology workup revealed pancreatic adenocarcinoma measuring $6.5 \times 4 \times 4$-cm (T2N1M0). Ca19-9 level was slightly elevated. A two-week regimen of radiotherapy combined with seven weeks of gemcitabine failed to alter the progress of the disease. The Ca19-9 level increased to 147 U/ml. The patient lost an additional 14-kg during this period and the treatment was considered a failure. Two days after returning home, he developed acute abdominal pain and was admitted to the hospital. Upon surgical examination, he was found to have a perforated duodenal ulcer. Severe peritonitis and fever followed his surgery. He subsequently developed pneumonia and recurrent high fevers. Despite a poor prognosis, after a month of hospitalization and with considerable weight loss, the patient was discharged to home care. Surprisingly, his recuperation and weight gain was rapid. A subsequent PET scan was negative for any focal disease and his tumour marker, Ca19-9, returned to the normal range. An ultrasound, however, revealed residual tumour, although it had regressed by approximately 70%. The patient regained an essentially normal life with excellent health for about a year, then he deteriorated and died 19 months following this febrile infection. Although treatment other than his prolonged infection may have contributed to his temporary regression, it appears significant that in this patient the duodenal perforation occurred in the vicinity of the tumour. This could have facilitated direct stimulation of the intra-tumoural stromal cell population. Perhaps longer regression could have been obtained for this patient *by simulating his feverous infection* through repeated booster inoculations with a killed vaccine prepared from the organism(s) that caused the peritoneal infection.

The duality of the effect of macrophages on tumour growth was well illustrated in an experiment comparing influence of stimulated and unstimulated macrophages on tumour growth. The investigators compared macrophages from normal and tumour-bearing mice on the growth of experimental tumours (fibrosarcoma, melanoma and lymphoma) *in vivo*. Both macrophage populations from normal and tumour-bearing mice were found to stimulate tumour growth. However, when an acute infection was mimicked through exposure of macrophages to killed bacteria (*Corynebacterium parvum*) the same macrophage populations were able to inhibit tumour growth in a dose dependent manner.[22]

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In the past, surgeons were known to deliberately establish suppurating sores following cancer surgery as a means of preventing recurrence. For example, the 19th century surgeon Verneuil would leave the incision open or loosely approximated with drainage, where suppuration would then ensue.[23] A student of Verneuil stated that "I was often struck by the slowness with which recurrence developed in such cases… I asked myself if suppuration, in eliminating the traces of cancer which had escaped the knife, did not play a role in delaying recurrence, and if therein lay the secret of success."[24] A more prudent method was later recommended in which a vaccine containing sterile bacteria would be injected into the surgical site following tumour removal. For example, in *Modern Operative Surgery*[25] (1943 edition), it was stated that following surgery for sarcoma of the limbs '*prophylactic injections of Coley's fluid* (a vaccine containing killed bacteria) *should be given in doses sufficient to cause a sharp febrile reaction*'. Such treatment with a sterile fluid containing a host of innate immune cell stimulators such as endotoxins, lipopolysaccharides, streptokinase and exotoxins (also known as superantigens) may be enough to shift the balance from repair to defense (Fig. 1), resulting in a more favorable post-surgical outcome.

This illustrates that the immune system may need to be challenged with factors it recognizes as *both foreign and dangerous* in order to induce an optimal response. A real feverous infection supplies both the *foreign* and *dangerous* components. How can we mimic this without exposing the patient to such an infection? Heat killed bacterial preparations may be useful as they can supply the *foreign* component but they do not supply a *danger* signal. However, coupling this vaccine with surgical procedures can potentially initiate an effective immune response against cancer. The combination of the two procedures exposes the intra-tumoural stromal cell population to a *danger* signal indicated by cellular death caused by the surgery and to a *foreign* component provided by the vaccine.

This is depicted in Fig. 1 by an increase in the defensive arm of the immune system. On the other hand, during cancer surgery (sterile wounding) *without the vaccine*, there is no *foreign* component and an increase in growth factor production from the stroma will attempt to '*heal the wound*', simultaneously promoting tumour growth. This would stimulate the reparative arm. Additional complications may arise when elective surgery, or any further sterile injury on 'cured' cancer patients activates dormant cancer cells as illustrated in the case of a 43-year-old male who had dormant lung cancer cells in his skull that became activated by minor accidental injury.[26] Presently, we cannot differentiate between former cancer patients that are really cured and those that have no evidence of disease, but carry dormant micrometastases. To be able to do this would be an important step forward.

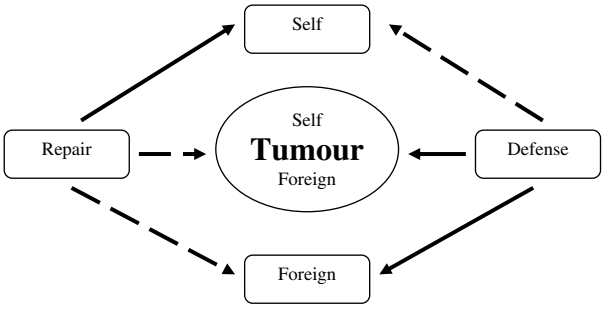

Fig. 1. This model illustrates the normal activity of the immune system engaged in repair of 'self' and defense against 'foreign' (solid lines). The relative balance of the two arms determines tumour growth, stable disease or regression. Growing tumours subvert stromal cells to produce growth factors for its own benefit by providing signals that mimic a continual wound healing process. This induces the reparative arm. Sterile surgical procedures can exacerbate this condition causing accelerated growth. An exogenous agent such as Coley's fluid can shift the balance to the defensive arm opposing this effect.

The differential effects of chronic and acute infections on subsequent cancer development further exemplify the opposing outcomes of repair or defense (Fig. 1). Chronic infections such as human papilloma virus (HPV) where there is continuous wounding without effective immune response, have been associated with an increased cancer risk over the long term.[8] In contrast, a history of frequent acute infections, where there is an effective immune response, have been associated with a reduced risk for subsequently developing cancer.[8]

The preceding examples illustrate that there is an extremely delicate balance in the dynamics of the tissue microenvironment as it relates to cancer, teetering precariously between growth promotion (wound healing), stable disease (dormant cancer), and cancer regression (stromal collapse and cellular cytotoxicity). This area needs more attention quickly, as the implications are far-reaching and significant.

Cancer diagnosis, surgery, or any procedure that has the potential to create significant sterile wounding should be treated with caution. These include mammographic compression, tissue biopsy, etc. These actions can stimulate the growth promoting (wound healing) factors in the microenvironment. For premenopausal women it may be advisable to perform such procedures after the follicular phase (day 8–12) of the menstrual cycle, as this phase is strongly growth promoting.[27] Also, advice might be given to *former* cancer patients to stay clear of work that has a high risk for physical injury, particularly compression injuries, such as may occur in logging, construction, etc. or, in choosing elective surgery. If such injuries do occur, immune system modifying agents may be administered during the recovery phase to minimize the risk of recurrence. There are also other issues to consider for cancer patients such as the use of anti-pyretics and prophylactic antibiotics since these agents will suppress immune system activation.

At the present time we do not advocate but rather discourage making any drastic changes to established diagnostic and surgical procedures. However, we believe it is timely and necessary to start discussing the issues presented here. It is understandable some may not receive this with enthusiasm as it is engraved in our medical psyche that infections and fevers should be avoided. In fact, such ideas may be viewed as a step backward in surgical progress. Indeed, a step backwards is sometimes needed to obtain a broader prospective.

Conflict of interest statement

JP van Netten and SA Hoption Cann have interests in a company that manufactures a sterile bacterial preparation.

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